DECLARATION UNDER RULE 132		
	Application #	09/622,199
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	First Inventor	SCHWARTZ
	Art Unit	1625
	Examiner	Seaman, D. Margaret
	Docket #	P06853US00/BAS

Commissioner for Patents
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S I R:

I, Jean-Charles SCHWARTZ, residing at 9 villa Seurat, 75014 Paris, France, declare and say as:

1. I am a citizen of France.

2. I am honorary Professor and Chairman at Université René Descartes in Paris, honorary member of the Institut Universitaire de France, member of the European Acadamy (Academia Europea), member of the French Academy of Sciences and author of over 700 publications in international journals.

3. I am an inventor of the above identified patent application. I am aware that the claims of the present patent application have been rejected for alleged lack of enablement.

4. The present patent application is directed to the treatment of disorders using a compound of formula IIa which acts as a ligand of the histamine H3 receptor. As a result, the compounds block the H3 receptor, enhance the release of histamine, increase the level of tele-methylhistamine (a major histamine metabolite), and treat diseases and disorders which benefit from activation of histaminergic neurons activity.

5. As stated in my January 8, 2003 Declaration, pharmological studies reported in the present application (pages 150-153 of the PCT application as published) clearly establish the interaction of compounds according to the claimed invention with the H3 receptor *in vitro* in rat and guinea pigs.

6. The compounds of the claimed invention are fully supported by the specification as to enable one pharmacologist of ordinary skill in the art to practice the invention as claimed. Therefore, no undue experimentation is necessary in order to practice the invention as claimed.

7. The present invention is based on the discovery by the present inventors that the claimed compounds can inhibit the binding of histamine to its H3 receptor as disclosed on page 66 – page 73 of the PCT application. The H3 receptor is mainly responsible for regulating synthesis and release of histamine in the synaptic gap; the inhibition therefore leads to higher rates of brain histamine release.

8. In order to be a suitable medicament, the candidate compounds must show the following activities:

- the ability to inhibit the binding of histamine to H3 receptor,
- the ability to be active after oral administration, and
- the ability to cross the blood brain barrier.

9. The efficacy after oral administration, blood brain barrier crossing ability and H3 receptor ligand activities can be evaluated together on a single *in vivo* animal model as recognized by many scientists in the field, which consists in measuring the brain tele-methylhistamine levels in orally treated rodents. Tele-methylhistamine is the major metabolite of histamine and the increase of its tissue levels reflects an increase of

histamine release and action. Accordingly, in our studies the compounds to be tested were orally administered to mice, and the tele-methylhistamine level in whole brain was then measured and compared to level in placebo-treated mice. From data obtained after administration of several doses (usually 4 to 5) of each compound to groups of 5 to 15 animals, ED50s were calculated. This calculation is accurate as the maximal increase obtained after administration of active compounds is generally about +100%, i.e. the signal/noise ratio is high.

10. Compound of Example 117 was found active at low dosage in this animal model and its activity was then confirmed in human patients (see the declaration previously filed with the Amendment of January 22, 2003). Consequently, this confirmation validates the predictability of the animal model used.

11. As a result, the animal pharmacological model enables one to safely predict that the compounds active in this test will have the desired activity in human patients.

12. In order to demonstrate that the claimed compounds have the claimed activities, namely to treat the claimed disorders and/or inhibit the H3 receptor, experiments were conducted where ED 50 values were recorded (table of paragraph 13 below) using the following method.

Male swiss mice (18-20g) are fasted 12h before p.o. administration. Animals are sacrificed 90 min after treatment and the brain is dissected out, homogenized in ice-cold perchloric acid (0.4 N). After centrifugation, supernatants are stored at -20°C. Tele-methylhistamine levels in the perchloric acid extract supernatants are measured by the radioimmunoassay described by Garbarg et al. (Eur. J. Pharmacol., 1989, 164, 1-11).

Increase of the tele-methylhistamine level measured are compared to the maximal effect induced by reference H_3-receptor antagonists such as thioperamide (Stark et al. J. Med. Chem. 1996, 39, 1220-1226) or ciproxifan (Ligneau et al. J. Pharmcol. Exp. Ther., 1996, 287, 658-666) given orally at the respective doses of 10 or 3 mg/kg.

13. ED 50 is expressed in mg/kg, following oral administration. The results below are given to illustrate the activity shown by the claimed compounds.

Examples	ED50 (mg/kg)
1	6.9
2	3.4
18	1.1
22	1.9
23	4.5
26	2.8
27	6.6
37	5.1
38	1.3
39	1.5
40	2.6
42	1.5
43	0.5
44	4.4
45	3.6
46	0.44
47	2
49	1.7
50	1
51	3
52	2
54	3.3
56	1.1
58	1.6
59	0.2
60	0.64
61	4.2
63	0.45

64	0.73
65	1.1
66	0.34
67	0.12
68	0.49
69	0.6
70	3.5
71	4.2
72	0.5
73	0.47
74	0.21
75	2.2
76	0.18
78	0.77
79	0.36
81	0.67
82	1.3
83	0.78
84	0.53
85	4.9
86	0.82
87	1.6
88	0.14
89	1.3
90	0.59
91	1.7
93	0.85
94	1.8
95	2.6
96	0.83
97	1.5
98	4.5
99	3.4
100	0.39
101	0.17
102	2.1
103	2.3
104	0.3
105	3.4
106	4
107	2.5
108	3.3
109	3.1
110	2.4
111	0.92

112	1.6
113	0.54
114	1.2
116	3.7
117	1.6
127	3.9
128	1.9
133	3.8
137	3.4
140	0.78
141	5.9
143	3.2
148	5.5
149	2.8
163	2.7

14. Since it is generally admitted that ED50 values in mice have to be divided by a factor of 5 to 10 to be transformed into preclinical corresponding values in human, the *in vivo* results given above provide evidence that all of the compounds of the invention are active in human. It is apparent from the results given above that the exemplified compounds of the invention show an *in vivo* activity similar or even better that compound of example 117. The clinical test carried out with respect to the compound of example 117 in human patient provides evidence that animal test are predictable of human activity. Therefore, these results establish evidence that all claimed compounds have the claimed activity.

15. In the Office Action mailed August 21, 2003, the Examiner alleges that the ED 50 values for the enumerated compounds of paragraph 13 differ greatly, yet in some cases the claimed compounds are only slightly different in structure, such that the activity is unpredictable based on structure and therefore there fails to be enablement for the claimed compounds. In fact, it should be underlined that all of the compounds recited have low ED50s (below 10 mg/kg and often below 1 mg/kg). This corresponds to

values very low in human and they are therefore all considered as very potent on criteria shared by all pharmacologists. The compounds have the claimed activity and can be used to treat the claimed disorders. Therefore, all of the claims are fully supported since the claimed Markush compound of formula IIa has the function of inhibiting H3 receptor activity by binding to the H3 receptor and therefore function to provide the claimed treatment.

16. Additionally, the test used for determining activity of the tested compounds is highly demanding and very selective. Namely, the compounds are administered by oral route, although activity is required in the brain area and passage of the blood/brain barrier is usually hardly achieved. Less active compounds could be identified by less selective conditions, for instance, by injection in brain (*icv*) or in circulation (iv). In fact, the present test requires the compound to be absorbed, to remain in circulation, to cross the blood-brain barrier and to stay within the brain until measurement is carried out, that is 90 minutes after treatment. By that time, the compound should not be metabolized or excreted. As each compound has distinct pharmacodynamics properties, the measurement at 90 minutes is not optimized. This means that compound can only be more active than the data presented in paragraph 13. In fact, the test is so devised that an activity identified by this test is sufficient for predicting a satisfactory activity. Compounds are generally considered active when ED50 are lower than 30mg/kg. As apparent from paragraph 13, the compounds of the invention all require only a fraction of this dose to be active. Consequently, the doses indicated in paragraph 13 are so low that the differences in activity do not affect predictability of the test. In fact, the doses listed in paragraph 13 are so low (largely less than 10mg/kg) for so many compounds

(for more than a hundred compounds), that it can be reasonably assumed that all compounds within the scope of the claims have an activity within the required range. The activities given in paragraph 13 are fully predictable for the compounds encompassed by the present claims.

17. For the sake of completeness, it is respectfully noted that all the conditions claimed derive from the H3 receptor activity. This was comprehensively discussed in the previously filed declaration filed January 22, 2003.

18. In order to assist the Examiner in locating the enabling disclosure in the specification, the following table summarizes the disclosure of the link between H3 receptor activity with the diseases and conditions listed in claim 89, with reference to articles numbered as 1-10 in the previously filed declaration of January 22, 2003.

Diseases or conditions of claim 89	Disclosure in Articles 1-10 of the declaration
CNS disorders	1
CNS disorders in aged persons	8 (abstract)
Psychotropic	6 (p. 403)
wakefulness, attention, memory, mood	1 (p. 27), 6 (p. 401), 7 (abstract), 8 (title + abstract), 1 (p. 30)
Obesity	1 (p. 29), 6 (p. 402)
Vertigo, motion sickness	1 (p. 27), 8 (abstract)
sedative, tranquility, anti-stress	1 (p. 27), 1 (p. 29)
Analgesic	1 (p. 27)
Antimigraine	1 (p. 27), 4,3 (abstract)
Psychosomatic	6 (p. 403)
respiratory, inflammatory, allergic, rheumatic conditions, asthma, inflammatory disorders, bronchitis, rhinitis, tracheitis, gastric or duodenal ulcers, ulcerative colitis, Crohn's disease, irritable bowel syndrome, cystitis, metritis, urinary and fecal incontinence, urticaria, itching, arthritis, conjunctivitis, premenstrual syndrome	4,3 (abstract), 5 (abstract)

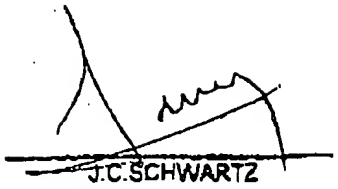
19. Cons quently, the specification as filed provides evidence in respect of the two following aspects:

- the compounds of the invention exhibit *in vivo* activity at low dosage on animals; this *in vivo* activity is predictable of the H3 activity on human patients; and
- the activities on the compounds of the invention on the conditions claimed are clearly linked with the demonstrated H3 activity.

20. The results of working examples, provided herewith, together with the prior art disclosing the link between H3 receptor and claimed conditions make the activities of the compounds as claimed, predictable. Moreover, the provided herewith examples establish proof that all claimed compounds possess the claimed H3 receptor activity inhibition. Consequently, based on the content of the disclosure of the prior art and the present specification, the skilled person in the art is provided with enough direction to work the invention and thus, the claimed invention is enabled in accordance with 35 U.S.C. § 112, first paragraph.

The undersigned declares further that all statements made herein of his knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 19 day of December 2003



J.C.SCHWARTZ